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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,501	12/31/2001	Etsuro Ogata	04853.0085	1393

22852 7590 08/25/2005

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,501	OGATA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-27* is/are pending in the application.

4a) Of the above claim(s) *12-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-11 and 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/7/05 has been entered.

2. Claims 1 and 4-27 are pending.

3. Claims 12-22 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1, 4-11 and 23-27, drawn to a method of maintaining or increasing low vasopressin level by administering to a patient at least one anti-PTHrP antibody or binding fragment thereof, are being acted upon in this Office Action.

5. Claim 11 is objected to for reciting non-elected embodiment.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 4-11, and 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of ameliorating low vasopressin level comprising administering to a patient a humanized antibody or antigen binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75, or antibody produced by hybridoma deposited as FERM BP-5631 wherein the antibody or binding fragment thereof inhibits the binding of parathyroid hormone related protein (PTHrP) to its PTHrP receptor, **does not** reasonably provide enablement for a method of maintaining or increasing low vasopressin level comprising administering to a patient at least one anti-PTHrP antibody, or binding fragment thereof such as any anti-PTHrP antibody, any modified form of

any antibody binding fragment, any humanized, or chimeric antibody, any antibody produced by the hybridoma deposited as FERM BP-5631, any monoclonal antibody, that inhibits the binding between PTHrP and a receptor thereof, allowing the antibody to inhibit the binding of PTHrP and its receptor and maintaining or increasing vasopressin level, (2) a method of treating at least any one symptom, any symptom such as polyuria, dehydration, mouth dryness, hyperosmolarity, caused by a decrease in vasopressin level as a results from cancer comprising administering to a patient at least any one anti-PTHrP antibody, any antibody fragment is bound to a carrier such as PEG, any antibody fragment is Fab, scFv, F(ab')2 or Fv as set forth in claims 1, 4-11, and 23-37. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of making antibody such as human, chimeric, humanized antibody and binding fragment thereof that binds specifically to the N terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75 for a method of inhibiting the binding of parathyroid hormone related protein (PTHrP) to its PTHrP receptor. The specification discloses administering humanized antibody that binds specifically to human PTHrP ameliorates the decreased blood vasopressin levels in mice implanted with human large cell lung carcinoma LC-6, a hypercalcemia model.

The specification does not teach how to make "modified form" of antibody that binds to *all* "PTHrP", much less which particular anti-PTHrP antibody maintains vasopressin level and which particular anti-PTHrP antibody increases vasopressin level in vivo. There is no showing in the specification as filed that administering any anti-PTHrP other than the specific humanized PTHrP antibody (Fig 1) resulted in increasing low vasopressin level of any patient. Likewise, there is no showing in the specification as filed that administering any anti-PTHrP resulted in

maintaining vasopressin level in vivo. In fact, the specification shows administering anti-PTHrP up to 3mg/kg has no significant effect on vasopressin levels, note the error bar among the treated and control group overlap (see Figure 3, in particular). The specification discloses that administering humanized PTHrP antibody has no effect on urine volume (Figure 2). However, at high concentration 3mg/kg, humanized anti-PTHrP treatment ameliorates increased blood osmotic pressure in the hypercalcemia rat.

Further, the specification does not teach any antibody such as monoclonal, humanized, chimeric, antibody fragment and modified form of said fragment that binds to the other part of PTHrP such as C-terminal part of all PTHrP, is effective for inhibiting binding between PTHrP and a receptor thereof, in turn, would be useful as a method of either maintaining or increasing low vasopressin level or a method of treating at least one symptom caused by a decrease in vasopressin level.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

It has been well known to those skilled in the art at the time the invention was made that minor structural differences in the antigen would change the binding specificity of the antibody. Kuby *et al*, of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. There is insufficient guidance as to which antigen such as PTHrP would produce antibody that binds to specifically to all PTHrP, in turn, would be useful for a method of maintaining low vasopressin level and which PTHrP antigen would produce antibody that would increase low vasopressin level.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See

abstract, in particular). Further, the specification discloses only monoclonal antibody that binds to human PTHrP (1-34) consisting of SEQ ID NO: 75, the binding specificity of other monoclonal antibody, fragment thereof, chimeric and humanized antibody are not enabled.

With regard to modified form of antibody binding fragment, there is insufficient guidance in the specification as filed as to which amino acids within the binding region of the antibody fragment (CDRs) to be modified by amino acid substitution, deletion, addition such that the resulting modified antibody fragment still maintains its binding specificity to human PTHrP.

Since the binding specificity of the antibody in the claimed methods is not enabled, it follows that any monoclonal antibody, chimeric antibody, and humanized antibody and binding fragment thereof that bind to *all* PTHrP for the claimed methods are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/7/05 have been fully considered but are not found persuasive.

Applicants' position is that new claim 26 recites an antibody that binds specifically to SEQ ID NO: 75. The full length PTHrP antigen is disclosed in the specification at page 5, line 19-21, in the Suva et al reference. The specification teaches how to make hybridoma, examples 1-2 (pages 19-23) teach administration of humanized anti-PTHrP antibody to human tumor-transplanted rats ameliorated decreased blood vasopressin levels, polyuria, and increased blood osmotic pressures, see Figure 1-4.

In response to applicant's argument that the full length sequence of the antigen is disclosed on page 5, line 19-21, it is note that the Suva et al reference discloses only human PTHrP, the claims encompass any antibody that binds to *any* PTHrP. However, the claims encompass methods of a method of *maintaining* or *increasing* low vasopressin level comprising administering to a patient at least any anti-PTHrP antibody, or binding fragment thereof such as

any anti-PTHrP antibody, any modified form of any antibody binding fragment, any monoclonal, humanized, or chimeric antibody that bind to any PTHrP, and antibody that binds specifically to SEQ ID NO: 75. The specification discloses only a method of making antibody such as human, chimeric, humanized antibody and binding fragment thereof that binds specifically to the N terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75 for a method of inhibiting the binding of parathyroid hormone related protein (PTHrP) to its PTHrP receptor to ameliorate the low vasopressin level.

The specification does not teach how to make "modified form" of any fragment of anti-PTHrP that binds to *all* "PTHrP", much less which particular anti-PTHrP antibody maintains vasopressin level and which particular anti-PTHrP antibody increases vasopressin level in vivo.

8. Claims 1, 4-11, and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for any antibody such as any monoclonal, humanized, chimeric, antibody fragment and any "modified form" of said fragment that binds to *all* "PTHrP" and *any* part of PTHrP other than N-terminal 1-34 of human PTHrP for a method of *maintaining* or *increasing* low vasopressin level.

The specification discloses only a method of making antibody such as human, chimeric, humanized antibody and binding fragment thereof that binds specifically to the N terminal 1-34 of human PTHrP consisting of the amino acid sequence of SEQ ID NO: 75 for a method of ameliorate low vasopressin level resulted from cancer. The specification discloses administering only humanized antibody that binds specifically to human PTHrP ameliorate the decreased blood vasopressin levels in mice implanted with human large cell lung carcinoma LC-6, a hypercalcemia model.

With the exception of the specific antibody mentioned above that binds specifically to the N-terminal of human PTHrP1-34 consisting of the amino acid sequence of SEQ ID NO: 75, and the hybridoma deposited as FERM BP-5631, there is insufficient written description about the binding specificity of all other antibody such as monoclonal, humanized, chimeric, and binding fragment thereof such as modified binding fragment thereof that bind to other PTHrP for the claimed method. There is inadequate written description about the structure of the CDRs of all

antibodies that correlate with functions such as which antibody maintains vasopressin levels while which antibody increases vasopressin levels upon administering to a patient. Further, there is insufficient written description about which amino acids within the binding fragment of any antibody to be modified by substitution, deletion, addition and/or combination thereof such that the "modified binding fragment" still maintains its binding specificity to human PTHrP of SEQ ID NO: 75.

Other than N-terminal of human PTHrP1-34 to which the antibody binds for the method of ameliorating low vasopressin level in a patient, the binding specificity of the antibody to other part of PTHrP1-34 other than terminal of human PTHrP1-34 in the claimed method is not adequately described. Given the lack of any additional parathyroid hormone related peptide (PTHrP) and C-terminal part of PTHrP to which the antibody binds, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of PTHrP to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 7/7/05 have been fully considered but are not found persuasive. Applicants' position is that that the structure of full-length PTHrP was known in the art at the time the application was filed. Further, the specification contains an actual reduction to practice of the claimed invention, which demonstrates that an anti-PTHrP antibody maintains or increases vasopressin level in an animal model of hypercalcemia. See specification at pages 19-24.

In response, the specification discloses only a method of ameliorating low vasopressin level by administering to a patient only antibody such as monoclonal antibody produced by hybridoma #23-57-154, #23-57-137-1, humanized, chimeric and antibody binding fragment thereof that binds specifically to *human* PTHrP. The specification discloses only *human* PTHrP and method of making antibody that binds to human PTHrP using the N terminal 1-34 amino acids of human PTHrP. Other than N-terminal part of human PTHrP to which the antibody binds for the claimed method, the rest of the PTHrP and the binding specificity of the antibody in the claimed method are not adequately described.

Given the lack of any additional parathyroid hormone related peptide (PTHrP) to which the antibody binds in the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicants' arguments filed 7/7/05 have been fully considered but are not found persuasive.

Applicants' position is that new claim 26 recites an antibody that binds specifically to SEQ ID NO: 75 and new claim 27 recites antibody that binds to human PTHrP. The full length PTHrP antigen is disclosed in the specification at page 5, line 19-21, in the Suva et al reference.

In response, claim 26 encompasses a method of maintaining or increasing low vasopressin level by administering to a patient at least any one anti-PTHrP antibody or binding fragment thereof.

The specification discloses only a method of making antibody such as human, chimeric, humanized antibody and binding fragment thereof that binds specifically to the N terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75 for a method of inhibiting the binding of parathyroid hormone related protein (PTHrP) to its PTHrP receptor to *ameliorate* the low vasopressin level. The specification shows administering anti-PTHrP up to 3mg/kg has no significant effect on vasopressin levels, note the error bar among the treated and control group overlap (see Figure 3, in particular). The specification discloses that administering humanized PTHrP antibody has no effect on urine volume (Figure 2). However, at high concentration 3mg/kg, humanized anti-PTHrP treatment ameliorates increased blood osmotic pressure in the hypercalcemia rat. There is no disclosure that administering any anti-PTHrP other than the specific humanized PTHrP antibody (Fig 1) resulted in increasing low vasopressin level of any patient. Likewise, there is no disclosure that administering any anti-PTHrP resulted in *maintaining* vasopressin level in vivo.

With the exception of the specific antibody mentioned above that binds specifically to the N-terminal of human PTHrP1-34 consisting of the amino acid sequence of SEQ ID NO: 75, and the hybridoma deposited as FERM BP-5631, there is insufficient written description about the binding specificity of all other antibody such as monoclonal, humanized, chimeric, and binding fragment thereof such as modified binding fragment thereof that to *other* PTHrP for the claimed method. There is inadequate written description about the structure of the CDRs of all antibodies

that correlate with functions such as which antibody maintains vasopressin levels while which antibody increases vasopressin levels upon administering to a patient. Further, there is insufficient written description about which amino acids within the binding fragment of any antibody to be modified by substitution, deletion, addition and/or combination thereof such that the "modified binding fragment" still maintains its binding specificity to human PTHrP of SEQ ID NO: 75.

Other than N-terminal of human PTHrP1-34 to which the antibody binds for the method of ameliorating low vasopressin level in a patient, the binding specificity of the antibody to other part of PTHrP1-34 other than terminal of human PTHrP1-34 in the claimed method is not adequately described. Given the lack of any additional parathyroid hormone related peptide (PTHrP) and C-terminal part of PTHrP to which the antibody binds, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of PTHrP to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 1, 4-8 and 23-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "maintaining or increasing low vasopressin level" in claims 1, 26 and 27 is ambiguous and indefinite because the term "maintaining the level of vasopressin" is not the same as increasing the low level of vasopressin level" since it appears to be mutually exclusive. Further, it is not clear administering which anti-PTHrP would result in maintaining the level of vasopressin and administering which anti-PTHrP would result in increasing vasopressin level. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The "at least one" in claims 1, 26 and 27 is ambiguous and indefinite because the term "at least one" suggesting there is another anti-PTHrP. The claims as written do not recite the other anti-PTHrP. Since the claims already recite a method ... "comprising", it is suggested that "at least one" be deleted from said claims.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 1, 5-11 and 26-27 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 6,903,194 (filed March 25, 1999: PTO 892).

The '194 patent teaches a method of treating at least one symptom such as hypercalcemia, polyuria, or dehydration, (see col. 1, lines 42-61, in particular) in patient with cancer that inherently caused low vasopressin level (see col. 60, line 6-18, in particular) by administering to the patient such as rat at least one anti-PTHrP antibody such as monoclonal antibody produced by the hybridoma deposited FERM BP-5631 (see claim 11 of the '194, col. 27, lines 29-36, Figure 12, in particular) or human antibody, chimeric or humanized antibody against PTHrP (see col. 24, lines 1-17, in particular) where the anti-PTHrP antibody inhibits the binding of PTHrP and its receptor (see claim 11 of the '194 patent). The reference symptoms are results from cancer (see col. 54, line 65 bridging col. 55, lines 19-26, in particular). The reference method inherently maintains or increase the level of vasopressin levels because the reference antibody used by the reference methods is the same antibody in the claimed method; the antibody is administered to the same patient population (patient with cancer) and the method step is the same as the claimed method step. Claims 26 and 27 are included in this rejection because the reference antibody binds specifically to human PTHrP 1-34, which is the same as the claimed SEQ ID NO: 75 (see col. 26, lines 44-50, in particular). Thus, the reference teachings anticipate the claimed invention.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1, 4 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,903,194 (filed March 25, 1999: PTO 892) in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629) or US Pat No. 4,946,778 (Aug 1990, PTO 892).

The teachings of the '194 patent have been discussed supra.

The claimed invention in claim 4 differs from the teachings of the reference only in that the method wherein the antibody is antibody fragment.

The claimed invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is Fab, F(ab')2.

Harlow et al teach a method of producing antibody fragment from any antibody such as Fab fragment or F(ab)2 (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody such as scFv or Fv (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce

the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as Fab or F(ab)2 as taught by Harlow et al or scFv as taught by the '778 patent using monoclonal, human antibody, chimeric or humanized antibody against PTHrP anti-PTHrP(1-34) that inhibits the binding between PTHrP and a receptor thereof as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application as taught by the '788 patent (See column 3, lines 33-48, in particular). The '194 patent teaches the reference antibody is useful for treating at least one symptom such as hypercalcemia, polyuria, or dehydration, that caused by cancer (see col. 1, lines 42-61, in particular) which resulted in inherent low vasopressin level (see col. 60, line 6-18, in particular)

17. Claims 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,903,194 (filed March 25, 1999: PTO 892) in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629) as applied to claims 1, 4 and 25 mentioned above and further in view of Kitamura et al (Biochem Biophys Res Commun 171(3): 1387-94, Sept 1990; PTO 892).

The combined teachings of the '194 patent and Harlow *et al* have been discussed supra.

The claimed invention in claim 23 differs from the combined teachings of the references only in that the method wherein the antibody fragment is bound to a carrier.

The claimed invention in claim 24 differs from the combined teachings of the references only in that the method wherein the antibody fragment is bound to a PEG.

Kitamura et al teach a method of conjugating antibody fragment such as F(ab')2 to a carrier such as polyethylene glycol (PEG) (see entire document, abstract, in particular). Kitamura et al teach that PEG-conjugated antibody fragment could be a promising carrier for use in targeting cancer chemotherapy because PEG-conjugated antibody fragment retains its antigen-binding activity, improves half life of the antibody fragment and increased accumulation in tumors (see abstract, in a particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the F(ab)2 that bound to a carrier such as PEG as taught by Kitamura for the Fab or F(ab)2 fragment that binds to PTHrP as taught by the '194 patent and Harlow at al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce antibody fragment bound to a carrier such as PEG because Kitamura et al teach that PEG-conjugated antibody fragment could be a promising carrier for use in targeting cancer chemotherapy since PEG-conjugated antibody fragment retains its antigen-binding activity, improves half life of the antibody fragment and increased accumulation in tumors (see abstract, in a particular).

18. Claims 1, 4, 7-11 and 25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto *et al* (Endocrinology 138(1): 383-388; PTO 892) in view of Sato *et al* (J Bone Miner Res 8(7): 849-60, 1993; PTO 1449), Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629) and Hotta et al (Endocr J 45(6): 773-8, Dec 1998; PTO 892).

Yamamoto *et al* teach a method of increasing low vasopressin level in a patient such as rat by administering to said patient at least one substance such as PTHrP(1-34) fragment (See Fig 1, in particular). The reference PTHrP inherently competes and thereby inhibiting the binding of the full length PTHrP to a receptor such as PTHrP receptor and PTH receptor and thereby increasing the vasopressin level (See page 387, column 2, third paragraph, in particular). The reference further teaches a method of maintaining vasopressin level by administering to the patient a substance such as a competitive antagonist to PTHrP such as PTHrP(7-34) (See Fig 2, page 387, column 2, last paragraph, in particular). The reference further teaches that arginine-

vasopressin (AVP) has anti-diuretic and pressor activity and is produced from hypothalamic magnocellular neurons in the suproptic nucleic (SON) and paraventricular nuclei of the brain (See page 383, column 2, second paragraph, in particular). Yamamoto et al further teach that centrally administered (iv) causes the secretion of AVP from the thalamus and the plasma AVP levels is similar to the levels observed after the restriction of water and food intake or hyperosmolarity induced by i.p. injection of hyperosmotic saline (See page 387, column 2, second paragraph, in particular).

The claimed invention in claim 1 differs from the teachings of the reference only that the method of maintaining or increasing low vasopressin level comprises administering to a patient at least one anti-PTHrP antibody that inhibits the binding between PTHrP and a receptor thereof.

The claimed invention in claim 4 differs from the teachings of the reference only that the method wherein the antibody is at least one of a fragment of an anti-PTHrP antibody.

The claimed invention in claim 7 differs from the teachings of the reference only that the method wherein the substance is a monoclonal anti-PTHrP antibody.

The claimed invention in claim 8 differs from the teachings of the reference only that the method wherein the low vasopressin level results from cancer.

The claimed invention in claim 25 differs from the teachings of the reference only that the method wherein the antibody is Fab or F(ab)2.

Sato *et al* teach malignancy associated hypercalcemia is mainly caused by excessive production of parathyroid hormone related protein (PTHrP) by tumor (See abstract, in particular). The symptoms of excess PTHrP include hypercalcemia, cachexia that is associated with polyuria, dehydration and hyperosmolarity due to hypercalcemia, and increasing osteoclastic bone resorption (See 849, in particular). Sato *et al* teach daily SC injection of anti-PTHrP 1-34 monoclonal antibody which inhibiting the binding between PTHrP and its receptor led to a decrease in serum calcium, increase in body weight and survival of nude mice bearing PTHrP producing tumors (See abstract, in particular). Sato et al teach that if a human monoclonal antibody against PTHrP(1-34) could be develop, then passive immunization would be potentially one of the most effective therapies associated with hypercalcemia due to excessive production of PTHrP.

Harlow et al teach a method of producing antibody fragment such as Fab fragment or F(ab)2 (See page 626-629, in particular). Harlow *et al* further teach that the problems of using

multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Hotta et al teach hypercalcemia in euthyroid patient with secondary hypoadranalism and diabetes insipidus due to hypothalamic tumor is associated with decrease in arginine vasopressin and symptoms caused by a decrease in vasopressin level includes polyuria, severe dehydration, disturbance of thirst sensation caused by the hypothalamic tumor (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the PTHrP(1-34) fragment that inhibits the binding between PTHrP and a receptor as taught by Yamamoto et al for the monoclonal antibody that binds to PTHrP(1-34) as taught by Sato et al or PTHrP(1-34) or antibody fragment such as Fab or F(ab)2 produced by the method as taught by Harlow et al for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Yamamoto et al teach that centrally administered (iv) PTHrP (1-34) causes the secretion of AVP from the thalamus and the plasma AVP levels is similar to the levels observed after the restriction of water and food intake or hyperosmolarity induced by i.p injection of hyperosmotic saline (See page 387, column 2, second paragraph, in particular). Sato *et al* teach malignancy associated hypercalcemia is mainly caused by excessive production of parathyroid hormone related protein (PTHrP) by tumor (See abstract, in particular) and monoclonal antibody to PTHrP (1-34) inhibits the binding between PTHrP and its receptor led to a decrease in serum calcium, increase in body weight and survival of nude mice bearing PTHrP producing tumors (See abstract, in particular). Hotta et al teach hypercalcemia in euthyroid patient with secondary hypoadranalism and diabetes insipidus due to hypothalamic tumor is associated with arginine vasopressin and symptoms caused by a decrease in vasopressin level includes polyuria, severe dehydration, disturbance of thirst sensation caused by the hypothalamic tumor (See abstract, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Applicants' arguments filed 7/7/05 have been fully considered but are not found persuasive.

Applicants' position is that while Sato et al. describes a PTHrP antibody, it does not teach vasopressin activity of the PTHrP antibody. Additionally, there are no teachings in Sato et al. of uses that would suggest a vasopressin effect for these antibodies. Instead, Sato et al focuses exclusively on malignancy-associated hypercalcemia, an unrelated condition.

Yamamoto et al teaches that PTHrP(1-34) causes the release of arginine-vasopressin through a novel receptor distinct from the PTH/PTHrP receptors described previously. Yamamoto et al. also teaches that this is a unique effect of this specific peptide, not shared by other related peptides. In Yamamoto et al., administration of PTHrP(1-34) resulted in an increase of arginine-vasopressin levels. Yet, administration of PTHrP(7-34) or PTH(1-34), a similar protein, had no significant effect on arginine-vasopressin levels. This establishes that PTHrP(1-34) is having a unique effect, which may very likely be distinct from normal PTH or PTHrP activities. Given that PTHrP(7-34) and PTH(1-34) did not affect arginine-vasopressin levels, it would not be obvious to one skilled in the ad that antibodies to PTHrP would increase vasopressin levels, as the arginine vasopressin effect is unique to one particular form of PTHrP. One skilled in the art would not have a reasonable expectation of success in using antibodies to PTHrP in general to modulate vasopressin levels. Neither Harlow et al. or Hotta et al. provide this reasonable expectation of success.

In response to applicant's argument that Sato et al does not to vasopressin effect using the reference PTHrP antibody, Yamamoto et al teaches that PTHrP(1-34) causes the release of arginine-vasopressin. Sato *et al* teach malignancy associated hypercalcemia is mainly caused by excessive production of parathyroid hormone related protein (PTHrP) by tumor (See abstract, in particular). In fact, the specification discloses that the decrease in vasopressin level and hypercalcemia are a result from tumor implantation (see page 20, first paragraph, in particular). Sato *et al* teach daily SC injection of anti-PTHrP 1-34 monoclonal antibody which inhibiting the binding between PTHrP and its receptor led to a decrease in serum calcium, increase in body weight and survival of nude mice bearing PTHrP producing tumors (See abstract, in particular). In fact, the specification discloses antibody to PTHrP1-34, the same antibody as that taught by Sato et al. Given that the claimed method use the same antibody in the same population model as taught by Sato et al, the claimed method obvious would have the same result as that taught by Sato et al. One of ordinary skill in the art would have an expectation of success that the anti-

PTHrP that inhibits binding of PTHrP to its receptor thereof taught by Sato et al and Yamamoto would have the same effect as the claimed method.

In response to applicant's argument that PTHrP(1-34) causes the release of arginine-vasopressin through a novel receptor distinct from the PTH/PTHrP receptors described previously, none of the claims recite that the anti-PTHrP antibody or binding fragment thereof inhibits the binding between PTHrP to any particular receptor. Further, the binding specificity of the anti-PTHrP in the claimed method is the same antibody as taught by the Sato et al and Yamamoto et al. Given the method treatment uses the same product to treat the same population, the method would obviously produce the same results using the same product.

19. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto *et al* (Endocrinology 138(1): 383-388; PTO 892) in view of Sato *et al* (J Bone Miner Res 8(7): 849-60, 1993; PTO 1449), Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629) and Hotta *et al* (Endocr J 45(6): 773-8, Dec 1998; PTO 892) as applied to claims 1, 4, 7-11 and 25 mentioned above and further in view of US Pat No. 6,180,370B (filed June 1995; PTO 892).

The combined teachings of Yamamoto *et al*, Sato *et al*, Harlow *et al* and Hotta *et al* have been discussed supra.

The claimed invention in claim 5 differs from the combined teachings of the references only in that the method wherein the antibody is a humanized or chimeric antibody.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular). The '370 patent further teaches that humanized immunoglobulin (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans and yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce humanized or chimeric antibody as taught by the '370 patent using the monoclonal antibody that binds specifically to PTHrP as taught by Sato et al or Harlow et al for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al or to treat symptoms associated with increased hypercalcemia and decrease in

vasopressin level as taught by Hotta et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce chimeric or humanized antibodies because the '370 patent teaches that the chimeric humanized immunoglobulin (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular). Sato et al teach that if a human monoclonal antibody against PTHrP(1-34) could be develop, then passive immunization would be potentially one of the most effective therapies associated with hypercalcemia due to excessive production of PTHrP.

Applicants' arguments filed 7/7/05 have been fully considered but are not found persuasive.

Applicants' position is that the '370 patent, does not teach or suggest that this antibody could be used to maintain or increase vasopressin levels.

In response, Yamamoto et al teaches that PTHrP(1-34) causes the release of arginine-vasopressin. Sato *et al* teach malignancy associated hypercalcemia is mainly caused by excessive production of parathyroid hormone related protein (PTHrP) by tumor (See abstract, in particular). In fact, the specification discloses that the decrease in vasopressin level and hypercalcemia are a result from tumor implantation (see page 20, first paragraph, in particular). Sato *et al* teach daily SC injection of anti-PTHrP 1-34 monoclonal antibody which inhibiting the binding between PTHrP and its receptor led to a decrease in serum calcium, increase in body weight and survival of nude mice bearing PTHrP producing tumors (See abstract, in particular). In fact, the specification discloses antibody to PTHrP1-34, the same antibody as that taught by Sato et al. Given that the claimed method use the same antibody in the same population model as taught by Sato et al, the claimed method obvious would have the same result as that taught by Sato et al. One of ordinary skill in the art would have an expectation of success that the anti-PTHrP that inhibits binding of PTHrP to its receptor thereof taught by Sato et al and Yamamoto would have the same effect as the claimed method.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33;

column 68 lines 8-44, in particular). The '370 patent further teaches that humanized immunoglobulin (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans and yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular). Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce humanized or chimeric antibody as taught by the '370 patent using the monoclonal antibody that binds specifically to PTHrP as taught by Sato et al or Harlow et al for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al or to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce chimeric or humanized antibodies because the '370 patent teaches that the chimeric humanized immunoglobulin (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular). Sato et al teach that if a human monoclonal antibody against PTHrP(1-34) could be develop, then passive immunization would be potentially one of the most effective therapies associated with hypercalcemia due to excessive production of PTHrP.

20. Claims 23-24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto *et al* (Endocrinology 138(1): 383-388; PTO 892) in view of Sato *et al* (J Bone Miner Res 8(7): 849-60, 1993; PTO 1449), Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629) and Hotta *et al* (Endocr J 45(6): 773-8, Dec 1998; PTO 892) as applied to claims 1, 4, 7-11 and 25 mentioned above and further in view of Kitamura et al (Biochem Biophys Res Commun 171(3): 1387-94, Sept 1990; PTO 892).

The combined teachings of Yamamoto *et al*, Sato *et al*, Harlow *et al* and Hotta *et al* have been discussed supra.

The claimed invention in claim 23 differs from the combined teachings of the references only in that the method wherein the antibody fragment is bound to a carrier.

The claimed invention in claim 24 differs from the combined teachings of the references only in that the method wherein the antibody fragment is bound to a PEG.

Kitamura et al teach a method of conjugating antibody fragment such as F(ab')2 to a carrier such as polyethylene glycol (PEG) (see entire document, abstract, in particular). Kitamura et al teach that PEG-conjugated antibody fragment could be a promising carrier for use in targeting cancer chemotherapy because PEG-conjugated antibody fragment retains its antigen-binding activity, improves half life of the antibody fragment and increased accumulation in tumors (see abstract, in a particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the F(ab)2 that bound to a carrier such as PEG as taught by Kitamura for the Fab or F(ab)2 fragment that binds to PTHrP as taught by Harlow at al and Sato *et al* for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al or to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce antibody fragment bound to a carrier such as PEG because Kitamura et al teach that PEG-conjugated antibody fragment could be a promising carrier for use in targeting cancer chemotherapy since PEG-conjugated antibody fragment retains its antigen-binding activity, improves half life of the antibody fragment and increased accumulation in tumors (see abstract, in a particular).

Applicants' arguments filed 7/7/05 have been fully considered but are not found persuasive.

Applicants' position is that the teaching of Kitamura does not cure the defects cited above. Specifically, the newly cited reference Kitamura does not teach or suggest that this antibody could be used to maintain or increase vasopressin levels.

In response, Yamamoto et al teaches that PTHrP(1-34) causes the release of arginine-vasopressin. Sato *et al* teach malignancy associated hypercalcemia is mainly caused by excessive production of parathyroid hormone related protein (PTHrP) by tumor (See abstract, in particular). In fact, the specification discloses that the decrease in vasopressin level and hypercalcemia are a result from tumor implantation (see page 20, first paragraph, in particular). Sato *et al* teach daily

SC injection of anti-PTHrP 1-34 monoclonal antibody which inhibiting the binding between PTHrP and its receptor led to a decrease in serum calcium, increase in body weight and survival of nude mice bearing PTHrP producing tumors (See abstract, in particular). In fact, the specification discloses antibody to PTHrP1-34, the same antibody as that taught by Sato et al. Given that the claimed method use the same antibody in the same model as taught by Sato et al, the claimed method obvious would have the same result as that taught by the Sato et al. One of ordinary skill in the art would have an expectation of success that the anti-PTHrP that inhibits binding of PTHrP to its receptor thereof taught by Sato et al and Yamamoto would have the same effect as the claimed method.

In response to applicant's argument that PTHrP(1-34) causes the release of arginine-vasopressin through a novel receptor distinct from the PTH/PTHrP receptors described previously, none of the claims recite that the anti-PTHrP antibody or binding fragment thereof inhibits the binding between PTHrP to any particular receptor. Further, the binding specificity of the anti-PTHrP in the claimed method is the same antibody as taught by the Sato et al and Yamamoto et al. Given the method treatment uses the same product to treat the same population, the method would obviously produce the same results using the same product.

The claimed invention in claim 23 differs from the combined teachings of the references only in that the method wherein the antibody fragment is bound to a carrier.

The claimed invention in claim 24 differs from the combined teachings of the references only in that the method wherein the antibody fragment is bound to a PEG.

Kitamura et al teach a method of conjugating antibody fragment such as F(ab')2 to a carrier such as polyethylene glycol (PEG) (see entire document, abstract, in particular). Kitamura et al teach that PEG-conjugated antibody fragment could be a promising carrier for use in targeting cancer chemotherapy because PEG-conjugated antibody fragment retains its antigen-binding activity, improves half life of the antibody fragment and increased accumulation in tumors (see abstract, in a particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the F(ab)2 that bound to a carrier such as PEG as taught by Kitamura for the Fab or F(ab)2 fragment that binds to PTHrP as taught by Harlow at al and Sato *et al* for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al or to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta et al. From the combined teachings of the references, it is

apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce antibody fragment bound to a carrier such as PEG because Kitamura et al teach that PEG-conjugated antibody fragment could be a promising carrier for use in targeting cancer chemotherapy since PEG-conjugated antibody fragment retains its antigen-binding activity, improves half life of the antibody fragment and increased accumulation in tumors (see abstract, in a particular).

21. Claim 25 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto *et al* (Endocrinology 138(1): 383-388; PTO 892) in view of Sato *et al* (J Bone Miner Res 8(7): 849-60, 1993; PTO 1449), Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629) and Hotta *et al* (Endocr J 45(6): 773-8, Dec 1998; PTO 892) as applied to claims 1, 4, 7-11 and 25 mentioned above and further in view of US Pat No. 4,946,778 (Aug 1990, PTO 892).

The combined teachings of Yamamoto *et al*, Sato *et al*, Harlow *et al* and Hotta *et al* have been discussed supra.

The claimed invention in claim 25 differs from the combined teachings of the references only in that the method wherein the antibody fragment is scFv or Fv.

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made with an expectation of success to make single chain antibody as taught by the '778 patent using the antibody that binds to PTHrP as taught by Sato *et al* or antibody fragments as taught by Sato et al and Harlow et al for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al or to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta et al. From the combined

teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.
One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Applicants' arguments filed 7/7/05 have been fully considered but are not found persuasive.

Applicants' position is that the '778 patent does not cure the defects cited above. Specifically, the newly cited reference, the '778 patent, does not teach or suggest that this antibody could be used to maintain or increase vasopressin levels.

In response, Yamamoto et al teaches that PTHrP(1-34) causes the release of arginine-vasopressin. Sato *et al* teach malignancy associated hypercalcemia is mainly caused by excessive production of parathyroid hormone related protein (PTHrP) by tumor (See abstract, in particular). In fact, the specification discloses that the decrease in vasopressin level and hypercalcemia are a result from tumor implantation (see page 20, first paragraph, in particular). Sato *et al* teach daily SC injection of anti-PTHrP 1-34 monoclonal antibody which inhibiting the binding between PTHrP and its receptor led to a decrease in serum calcium, increase in body weight and survival of nude mice bearing PTHrP producing tumors (See abstract, in particular). In fact, the specification discloses antibody to PTHrP1-34, the same antibody as that taught by Sato et al. Given that the claimed method use the same antibody in the same model as taught by Sato et al, the claimed method obvious would have the same result as that taught by the Sato et al. One of ordinary skill in the art would have an expectation of success that the anti-PTHrP that inhibits binding of PTHrP to its receptor thereof taught by Sato et al and Yamamoto would have the same effect as the claimed method.

In response to applicant's argument that PTHrP(1-34) causes the release of arginine-vasopressin through a novel receptor distinct from the PTH/PTHrP receptors described previously, none of the claims recite that the anti-PTHrP antibody or binding fragment thereof inhibits the binding between PTHrP to any particular receptor. Further, the binding specificity of

the anti-PTHrP in the claimed method is the same antibody as taught by the Sato et al and Yamamoto et al. Given the method treatment uses the same product to treat the same population, the method would obviously produce the same results using the same product. One having ordinary skill in the art at the time the invention was made with an expectation of success to make single chain antibody as taught by the '778 patent using the antibody that binds to PTHrP as taught by Sato *et al* or antibody fragments as taught by Sato et al and Harlow et al for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al or to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta et al. One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

24. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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